In the Claims

Please amend the claims presented during the international phase as follows. Applicant presents a full set of claims showing markups of the claims with insertions and deletions indicated by underlining (or double bracketing) and strikethrough text, respectively. Claims presented in the international phase are indicated as "original" herein; please note, however, that some of these claims were amended during the international phase.

1. (Original) A genetically modified non-human mammal or cell characterised in that it does not comprise a nucleic acid sequence which itself encodes any endogenous immunoglobulin heavy chain constant region locus polypeptide and in that one or more endogenous Ig H Variable region, one or more endogenous Ig H D segment, and one or more endogenous Ig H J segment nucleic acid sequences are present.

2. (Original) A genetically modified non-human mammal or cell characterised in that it does not comprise a nucleic acid sequence which itself encodes any endogenous immunoglobulin heavy chain constant region locus polypeptide and in that all the endogenous Ig H Variable region, D and J segment nucleic acid sequences are present.

3. (Currently amended) A genetically modified non-human mammal or cell according to claim 1 ~~or claim 2~~ characterised in that it does not comprise a nucleic acid sequence which itself encodes any immunoglobulin heavy chain constant region (IgH C) polypeptide.

4. (Currently amended) A genetically modified non-human mammal or cell according to claim 1 ~~any of claims 1 to 3~~ characterised in that all immunoglobulin heavy chain constant region gene sequences are absent or partially absent from the genome.

5. (Currently amended) A genetically modified non-human mammal or cell according to claim 1 ~~any of the preceding claims~~, characterised in that it is obtainable or obtained by targeted deletion of essentially all endogenous IgH C gene sequences.

6. (Currently amended) A genetically modified non-human mammal or cell according to claim 1 ~~any of the preceding claims~~ characterised in that it is obtainable or obtained by Cre *lox*P recombination.

7. (Currently amended) A genetically modified non-human mammal or cell according to claim 1 ~~any of the preceding claims~~ characterised in that at least part of at least one IgH C gene enhancer sequence is present.

8. (Currently amended) A genetically modified non-human mammal or cell according to claim 1 ~~any of the preceding claims~~ characterised in that a non-endogenous site-specific recombination sequence is present within the genome.

9. (Original) A genetically modified non-human mammal or cell characterised by having a non-endogenous site-specific recombination sequence downstream of, or within the last gene of the IgH C locus.

10. (Original) A genetically modified non-human mammal or cell according to claim 8 characterised by having a further non-endogenous site specific recombination sequence upstream of, or within the first gene of the IgH C locus.

11. (Currently amended) A genetically modified non-human mammal or cell according to claim 1 ~~any of the preceding claims~~ characterised in that one or more selectable marker(s) is present within the genome.

12. (Original) A genetically modified non-human mammal or cell according to claim 8 characterised in that at least one selectable marker is present upstream of, or downstream of, the non-endogenous site specific recombination sequence.

13. (Original) A genetically modified non-human mammal or cell according to claim 9 characterised in that at least one selectable marker is integrated within the genome upstream of, and/or downstream of, at least one non-endogenous site specific recombination sequence.

14. (Currently amended) A genetically modified non-human mammal or cell according to claim 11 ~~any of claims 11 to 13~~ characterised in that the selectable marker(s) is one or more selectable marker selected from a group comprising a neomycin resistance gene, a puromycin resistance gene, and a hygromycin resistance gene.

15. (Currently amended) A genetically modified non-human mammal or cell according to claim 7 ~~any of claims 7 to 14~~ characterised in that the non-endogenous site-specific recombination sequence is a *lox*P site.

16. (Currently amended) A genetically modified non-human mammal according to claim 1 ~~any of the preceding claims~~ characterised in that it is a mouse.

17. (Currently amended) A genetically modified non-human cell according to claim 1 ~~any of claims 1 to 15~~ characterised in that it is a mouse cell.

18. (Currently amended) A genetically modified mouse according to claim 16, ~~or a genetically modified mouse cell according to claim 17,~~ characterised in that all eight endogenous IgH C genes μ, δ, γ3, γ1, γ2a, γ2b, ε and α are absent or partially absent.

19. (Currently amended) A genetically modified non-human cell according to claim 1 ~~any of claims 1 to 15 or claim 17 or 18~~ characterised in that it is an embryonic stem cell.

20. (Currently amended) A genetically modified non-human mammal derived from a genetically modified non-human mammal of claim 1 ~~any of claims 1 to 16 or claim 18~~.

21. (Currently amended) A genetically modified non-human mammal derived from a genetically modified non-human cell of claim 1 ~~any of claims 1 to 15 or any of claims 17 to 19~~.

22. (Currently amended) A genetically modified non-human cell derived from a genetically modified non-human mammal of claim 1 ~~any of claims 1 to 16 or claim 18~~.

23. (Original) A method for producing a genetically modified non-human cell comprising:

(a) (i) transfecting a non-human cell with a targeting construct for integration upstream of, or within the first IgH C gene of the IgH C locus, said targeting construct comprising a non-endogenous site specific recombination sequence and a selectable marker, selecting for a cell in which the selectable marker is present and screening said cell for integration of the recombination sequence, and,

(ii) transfecting a cell produced in (a)(i) with a targeting construct for integration downstream of, or within the last IgH C gene of the IgH C locus, said targeting construct

comprising a selectable marker and a non-endogenous site-specific recombination sequence, selecting for a cell in which the selectable marker is present and screening said cell for integration of the recombination sequence; or

(b) (i) transfecting a non-human cell with a targeting construct for integration downstream of, or within the last IgH C gene of the IgH C locus, said targeting construct comprising a non-endogenous site-specific recombination sequence and a selectable marker selecting for a cell in which the selectable marker is present, and screening said cell for integration of the recombination sequence, and

(ii) transfecting a cell produced in (b)(i) with a targeting construct for integration upstream of, or within the first IgH C gene of the IgH C locus, said targeting construct comprising a non-endogenous site-specific recombination sequence and a selectable marker, selecting for a cell in which the selectable marker is present, and screening said cell for integration of the recombination sequence; or

(c) co-transfecting a non-human cell with a targeting construct for integration upstream of, or within the first IgH C gene of the IgH C locus and with a targeting construct for integration downstream of, or within the last IgH C gene of the IgH C locus, each of said targeting constructs comprising a non-endogenous site specific recombination sequence and each having a selectable marker, selecting for a cell in which the selectable marker(s) is/are present, and screening said cell for integration of the recombination sequence; and optionally,

(d) providing to a cell obtained in (a)(ii), (b)(ii) or (c) a recombinase active at the non-endogenous site-specific recombination sequence and, optionally, screening for deletion events.

24. (Original) A method according to claim 23 characterised in that the non-endogenous site-specific recombination sequence is a *lox*P site.

25. (Original) A method according to claim 24 characterised in that, in optional step (d), the recombinase is a Cre recombinase.

26. (Currently amended) A method according to claim 23 ~~any of claims 23 to claim 25~~ characterised in that the recombinase is provided by an expression vector.

27. (Currently amended) A method according to claim 23 ~~any of claims 23 to 26~~ characterised in that the genetically modified non-human cell is a mouse cell.

28. (Currently amended) A method according to claim 23 ~~any of claims 23 to 27~~ characterised in that the genetically modified non-human cell is an embryonic stem cell.

29. (Canceled)

30. (Currently amended) A method for producing a genetically modified non-human mammal characterised in that an embryonic stem cell of claim 19 ~~or obtainable by a method of claim 28~~ is introduced into a host blastocyst and developed into a chimaeric animal.

31. (Currently amended) A method for producing a genetically modified non-human mammal ~~according to claim 30~~ characterised by:

(a) introducing a non-human mammal embryonic stem cell according to claim 19 ~~or obtainable by a method of claim 28~~ into a compatible non-human mammal blastocyst, and

(b) transplanting the blastocyst obtained in (a) into a compatible non-human mammal foster mother to obtain a chimaeric non-human mammal, and optionally, screening for the selectable marker(s), and/or the non-endogenous site specific recombination sequence(s), and/or for deletion of essentially all endogenous IgH C gene sequences.

32. (Currently amended) A method for producing a genetically modified non-human mammal characterised in that the chimaeric non-human mammal according to claim 30 ~~or claim 31~~ is bred to obtain heterozygous progeny.

33. (Original) A method for producing a genetically modified non-human mammal characterised in that the heterozygous progeny of claim 32 is inter-bred to obtain homozygous progeny.

34. (Original) A method for producing a genetically modified non-human mammal characterised by cross-breeding a genetically modified non-human mammal homozygous for integration of a non-endogenous site-specific recombination sequence upstream of, or within the first IgH C gene of the IgH C locus with a compatible genetically modified non-human mammal homozygous for integration of a non-endogenous site-specific recombination

sequence downstream, or within the last IgH C gene of the IgH C locus, to obtain heterozygous progeny and optionally interbreeding the heterozygous progeny to obtain progeny homozygous for both integrations.

35. (Original) A method according to claim 34 characterised by further comprising cross-breeding progeny homozygous for both integrations with a compatible non-human mammal capable of expressing a recombinase active at the non-endogenous site specific recombination sequence to obtain progeny; and optionally screening the progeny obtained for IgH C gene deletion.

36. (Currently amended) A method according to claim 34 ~~or claim 35~~ characterised in that the non-endogenous site specific recombination sequence(s) are *lox*P sites.

37. (Original) A method according to claim 36 characterised in that the recombinase is a Cre recombinase.

38. (Original) A method according to claim 36 characterised by further comprising cross-breeding progeny heterozygous or homozygous for *lox*P at both loci with a compatible non-human mammal capable of expressing Cre recombinase to obtain a progeny non-human mammal that does not comprise a nucleic acid sequence which itself encodes any endogenous Ig heavy chain constant region polypeptide on one or both alleles.

39. (Currently amended) A genetically modified non-human mammal characterised in that it is obtainable or obtained by a method of claim 35 ~~to claim 38~~ and does not comprise a nucleic acid sequence which itself encodes any endogenous Ig heavy chain constant region polypeptide and in that one or more endogenous Ig H Variable region, one or more endogenous Ig H D segment, and one or more endogenous Ig H J segment nucleic acid sequences are present.

40. (Currently amended) A genetically modified non-human mammal characterised in that it is obtainable or obtained by a method of claim 35 ~~to claim 39~~ and does not comprise a nucleic acid sequence which itself encodes any endogenous Ig heavy chain constant region polypeptide and that all the endogenous Ig H Variable region, D and J segment nucleic acid sequences are present.

41. (Currently amended) A method for producing a genetically modified non-human mammal capable of expressing one or more exogenous genes, characterised by breeding a genetically modified non-human mammal according to claim 1 ~~claims 1 to 7 or claims 10 to 16 or claims 18 to 21~~ that does not comprise a nucleic acid sequence which itself encodes any endogenous immunoglobulin heavy chain constant region polypeptide, with a compatible non-human mammal that encodes and is capable of expressing one or more exogenous gene(s), to obtain progeny heterozygous for the one or more exogenous gene(s), and optionally inter-breeding the heterozygous progeny to produce progeny homozygous for the one or more exogenous gene(s).

42. (Currently amended) A method for producing a genetically modified non-human mammal or cell capable of expressing one or more exogenous gene(s) characterised by comprising introduction of one or more exogenous gene(s) into a non-human mammalian cell according to claim 1 ~~claims 1 to 7 or claims 10 to 15 or claims 17 to 21~~ that does not comprise a nucleic acid sequence which itself encodes any endogenous immunoglobulin heavy chain constant region polypeptide.

43. (Original) A method according to claim 42 characterised in that the non-human mammalian cell is an embryonic stem cell.

44. (Original) A method according to claim 43, characterised in that the one or more exogenous gene(s) are introduced by transfection.

45. (Original) A method according to claim 42 characterised in that the non-human mammal cell is an oocyte (egg cell).

46. (Original) A method according to claim 45, characterised in that the one or more exogenous gene(s) are introduced by DNA micro-injection.

47. (Currently amended) A method according to claim 42 ~~any of claims 42 to 46~~ characterised in that the one or more exogenous gene(s) are inserted into the genome of the non-human mammal or cell.

48. (Original) A method according to claim 47 characterised in that the one or more exogenous gene(s) are inserted into a non-endogenous site specific recombination sequence.

49. (Original) A method for producing a genetically modified non-human mammal capable of expressing one or more exogenous gene(s) characterised by cross-breeding a non-human mammal that does not comprise a nucleic acid sequence which itself encodes any endogenous immunoglobulin heavy chain constant region polypeptide and in that one or more endogenous Ig H Variable region, one or more endogenous Ig H D segment, and one or more endogenous Ig H J segment nucleic acid sequences are present with a transgenic mammal having one or more exogenous gene(s) associated with or flanked by a non-endogenous site specific recombination sequence and having a recombinase active at the non-endogenous site specific recombination sequence to obtain progeny and optionally screening the progeny for insertion of the one or more exogenous gene(s).

50. (Currently amended) A method for producing a genetically modified non-human mammal capable of expressing one or more exogenous gene(s) characterised by cross-breeding a non-human mammal that does not comprise a nucleic acid sequence which itself encodes any endogenous immunoglobulin heavy chain constant region polypeptide and in that all the endogenous Ig H Variable region, D and J segment nucleic acid sequences are present with ~~present.with~~ a transgenic mammal having one or more exogenous gene(s) associated with or flanked by a non-endogenous site specific recombination sequence and having a recombinase active at the non-endogenous site specific recombination sequence to obtain progeny and optionally screening the progeny for insertion of the one or more exogenous gene(s).

51. (Currently amended) A method according claim 46 ~~any of claims 46 to 50~~ characterised in that the non-endogenous site specific recombination sequence is a *loxP* sequence and insertion is by Cre – *lox P* integration.

52. (Currently amended) A method according to claim 41 ~~any of claims 41 to 51~~ characterised in that the genetically modified non-human mammal is a mouse.

53. (Currently amended) A method according to claim 41 ~~any of claims 41 to 52~~ characterised in that the exogenous gene or genes is an Ig H gene or Ig H genes.

54. (Original) A method according to claim 53 characterised in that the Ig H gene or genes is an IgH C gene or IgH C genes.

55. (Currently amended) A method according to claim 41 ~~any of claims 41 to 54~~ characterised in that the exogenous genes or genes are a human gene or human genes.

56. (Currently amended) A method according to claim 41 ~~any one of claims 41 to 55~~ characterised in that the exogenous genes are a human Ig heavy chain locus having V, D, J and/or C regions.

57. (Original) A method according to claim 56 wherein the human Ig heavy chain locus V, D, J and/or C regions are in germline configuration.

58. (Original) A method according to claim 56 wherein the human Ig heavy chain locus V, D, J and/or C regions are productively arranged.

59. (Currently amended) A non-human mammal or cell obtainable by a method of claim 41 ~~any of claims 41 to 58~~.

60.-61. (Canceled)

62. (Original) A method for production of exogenous immunoglobulin comprising use of a non-human mammal or cell according to claim 59.

63. (Original) A method for production of human immunoglobulin comprising use of a non-human mammal or cell according to claim 59.

64. (Currently amended) A method ~~or use~~ according to claim 62 ~~any one of claims 60 to 63~~ wherein the non-human mammal is a rodent.

65. (Currently amended) A method ~~or use~~ according to claim 62 ~~any one of claims 60 to 63~~ wherein the non-human mammal is a mouse.

66. (Currently amended) A method ~~or use~~ according to claim 62 ~~any one of claims 60 to 63~~ wherein the non-human cell is a rodent cell.

67. (Currently amended) A method ~~or use~~ according to claim 62 ~~any one of claims 60 to 63~~ wherein the non-human cell is a mouse cell.

68. (Currently amended) An immunoglobulin obtainable or obtained by a method according to claim 62 ~~any one of claims 62 to 67~~.

69. (Currently amended) A human immunoglobulin obtainable or obtained by a method according to claim 62 ~~any one of claims 62 to 67~~.

70.-71. (Canceled)

72. (Currently amended) A medicament composition comprising an immunoglobulin according to claim 68 ~~or claim 69~~ and a pharmaceutically acceptable excipient.

73. (New) A genetically modified mouse cell according to claim 17, characterised in that all eight endogenous IgH C genes μ, δ, γ3, γ1, γ2a, γ2b, ε and α are absent or partially absent.